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Genetic Markers of Fibrinolytic Responses of Older Persons to Exercise Training

Abstract

We assessed the interactive effect of genetic polymorphisms and exercise training on fibrinolysis in 50 – 75 yr old men (n = 17) and women (n = 28). Subjects had tissue plasminogen activator (t-PA) antigen levels and activity and plasminogen activator inhibitor-1 (PAI-1) activity measured before and after 6 mo of endurance-exercise training. Subject's DNA was typed for the PAI-1 4 G/5 G and t-PA I/D variants. Baseline PAI-1 activity, t-PA activity, and t-PA antigen levels were not different among PAI-1 or t-PA genotype groups. Overall, exercise training did not change PAI-1 activity (– 0.43 ± 0.81 IU/mL, p = NS), increased t-PA activity (0.37 ± 0.16 IU/mL, p = 0.02), and decreased t-PA antigen levels (– 0.88 ± 0.20 ng/mL, p < 0.001). Although the differences in changes with training were not significant among genotype groups, significant t-PA antigen level improvements were evident only in PAI-1 4 G allele carriers and significant t-PA activity increases only in PAI-1 4 G homozygotes. t-PA genotype affected the training-induced t-PA antigen level improvements (p = 0.033) after covarying for gender and baseline t-PA antigen levels, with the smallest and largest reductions in the D homozygotes and I/D heterozygotes, respectively. These findings could have important treatment implications for the use of exercise training to reduce CV disease and thrombotic risk in older men and women.

Key words
PAI-1 activity · t-PA antigen · PAI-1 genotype · t-PA genotype

Introduction

Impaired endogenous fibrinolysis, the inability to lyse excess or inappropriate clots, is an independent risk factor for cardiovascular (CV) disease. Fibrinolysis is primarily determined by the levels of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1). Elevated PAI-1 activity is associated with a greater risk for myocardial infarction and death [4,12,18]. Large-scale studies indicate that elevations in t-PA antigen, a marker for hypofibrinolysis predominantly reflecting inactive circulating t-PA bound to PAI-1, is related to myocardial infarction (MI) and stroke risk [4,22,23].

PAI-1 activity has been reported to be associated with a common 4 G/5 G PAI-1 genetic polymorphism in the PAI-1 gene promoter region [5]. This functional polymorphism has been shown to influence PAI-1 levels both in vitro and in vivo. Eriksson et al. [9] demonstrated that basal PAI-1 transcription varied as a function of PAI-1 genotype and PAI-1 levels were positively related to the number of 4 G alleles. Based on these and other results, the 4 G/5 G polymorphism has been considered an independent CV disease risk factor.

An Alu repeat insertion/deletion (I/D) polymorphism in intron 8 of the t-PA gene is also a locus that could affect fibrinolysis. A re-

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cent study found an independent relationship between the t-PA gene I allele and risk of nonfatal MI [28]. However, in another study, the t-PA gene D allele was related to venous thromboembolism risk [15], although they found no relationship between the t-PA gene I/D polymorphism and t-PA antigen levels. Interestingly, Jern and coworkers [17] found a significant relationship between t-PA vascular release rate, but not blood t-PA levels, and I/D genotype.

Studies of physical activity and CV disease incidence indicate that there is an unexplained protective effect of physical activity on CV disease after accounting for its effects on conventional CV disease risk factors [2]. It is generally believed that the positive effect of physical activity on CV health may be partly mediated via improvements in fibrinolysis [25]. Although the effects of exercise training on fibrinolysis have been investigated [3,6,8, 11,21,24,25], the results are not consistent. These discrepant findings may be attributed to different study designs, control of confounding variables, sample sizes, and the duration and intensity of exercise training. However, it is also possible that the genetic makeup of the subjects in these different studies varied.

To our knowledge, only one study has assessed whether individuals with different genetic makeup have different fibrinolytic responses to exercise training [26]. Vaisanen et al. reported that only PAI-1 4 G/4 G genotype men improved PAI-1 activity with exercise training. Therefore, we hypothesized that the PAI-1 4 G/5 G and the t-PA I/D polymorphisms would affect fibrinolytic responses to endurance exercise training.

Methods

Subjects were sedentary, non-smoking, healthy men (n = 17) and women (n = 28) aged 50 – 75 years; 32 of the subjects were Caucasian (13 men, 19 women), 10 were African American (3 men, 7 women), 2 were Asian/Pacific Islanders (1 man, 1 woman), and one woman was Hispanic American. Sedentary was defined as not having participated in regular aerobic activity (< 20 min, ≤ 2 times/wk) for ≥ 6 months. Written informed consent was provided by each subject after the study and its risks had been described. The study protocol was approved by the University of Maryland College Park Institutional Review Board. All women were postmenopausal; women on hormone replacement therapy (HRT) (n = 10) continued their HRT for the duration of the study and those not on HRT (n = 18) remained off for the duration of the study. Subjects were screened with a medical history and general physical examination. Screening for blood chemistry ensured no diabetes, liver, renal, or hematological diseases. Individuals with blood pressure > 160/90 mm Hg were excluded from the study. This project was part of a larger study for which subjects had to have ≥ 1 National Cholesterol Education Program plasma lipoprotein-lipid risk factor (cholesterol > 200 mg/dL, LDL-cholesterol > 140 mg/dL, HDL-cholesterol < 40 mg/dL, TG > 200 mg/dL). To screen for CV disease, a graded exercise test was administered and those with ECG or symptomatic evidence of CV disease were excluded from the study [1].

Subjects then underwent a 6 wk Dietary Stabilization program based on the American Heart Association Step 1 Diet [19]. Subjects maintained this diet throughout the study. To monitor adherence to the diet, 7-day food records were administrated before, during, and at the end of the exercise intervention. After completing Dietary Stabilization, subjects underwent baseline testing that included blood samples for plasma fibrinolytic measures (PAI-1 activity, t-PA activity, and t-PA antigen levels) and plasma lipoprotein lipid profiles, and measurement of $\dot{V}O_2$max.

Blood samples for fibrinolytic levels were collected between 6 : 30 and 9 : 30 AM after a 12-hr overnight fast to avoid the effect of circadian variation on fibrinolysis. Subjects were questioned to ensure they were free from any inflammation or infection for > 2 wks before blood sampling. Blood was collected through an atraumatic venipuncture. To determine PAI-1 and t-PA activities, blood was drawn into a tube containing acidified citrate buffer (Biopool Stabilyte, Biopool, Sweden). To determine t-PA antigen, blood was drawn into a tube containing 3.8% trisodium citrate. Within 15 min of collection, anticoagulated blood samples were centrifuged at 10,000 rpm for 20 min at 4 °C. After centrifugation, plasma was stored at – 80 °C until analysis. PAI-1 and t-PA activity assays were performed within 6 months of sample collection. Baseline and final samples were analyzed for t-PA antigen levels in the same assay run at the end of the study.

Platelet poor plasma PAI-1 activities were assayed by the chromogenic method (Spectrolyse/pL PAI, Biopool, Sweden). The intra-assay and inter-assay coefficients of variation (CV) for PAI-1 activity were 5.8% and 8.6%, respectively. Plasma t-PA activity was determined by the direct amidolytic activity method (Coaset t-PA, Chromogenix); intra-assay and inter-assay CV were 5.5% and 1.8%, respectively. Plasma t-PA antigen concentration was determined by enzyme-linked immunosorbent assay (ELISA) (Asserachrom, Diagnotica Stago); intra-assay and inter-assay CV were 3.9% and 2.8%, respectively.

$\dot{V}O_{2max}$ was measured during a graded treadmill protocol we have used previously [29]. A true $\dot{V}O_{2max}$ was considered to have been achieved if standard physiological criteria were exceeded [29]. Genomic DNA was extracted from leukocytes using a standard salting-out procedure. Genotype analysis for the PAI-1 promoter polymorphism was performed as described by Margaglione et al. [20]. Genotyping was performed according to Jern et al. [17] for the t-PA intron 8 I/D polymorphism.

The exercise training program consisted of endurance exercise 3 times/wk for 6 months under the supervision of study personnel with intensity and duration gradually increased so that subjects exercised for 40 min at 70% $\dot{V}O_{2max}$ for the last 3 – 4 months of training [29]. After 10 weeks, subjects added a lower intensity exercise bout on the weekend. After training, each subject repeated the measurements of plasma fibrinolytic levels, plasma lipoprotein-lipid profiles, and $\dot{V}O_{2max}$. To avoid the acute effects of exercise, blood samples during final testing were drawn 24 – 36 hrs after the last bout of exercise.

PAI-1 and t-PA genotype frequencies were compared to expected population frequencies using chi-squared tests. The distributions of men and women, and women who were on and not on HRT were also compared among genotype groups using chi-squared

tests. Ethnicity was included as a covariate in all initial analyses; however, there were no significant effects associated with ethnicity and including ethnicity had no significant effects on fibrinolysis outcome variables. Differences for variables among PAI-1 and t-PA genotype groups were analyzed by one-way ANOVA. Homogeneity of variance was violated only for baseline BMI among t-PA genotype groups and these values were analyzed using an ANOVA on appropriately transformed data. Changes in fibrinolytic variables with training among genotype groups were analyzed by ANCOVA using general linear models; specific covariates used for each analysis are provided in the Results section. When group differences existed, appropriate post hoc tests were performed. Statistical analyses were performed using the SPSS 10.0 program (SPSS Inc, Chicago, USA). Data are presented as mean ± SE. A p-value < 0.05 was considered statistically significant.

Results

Allele and genotype frequencies (Table 1)

In the total population, 4 G and 5 G allele frequencies for the PAI-1 promoter gene variant were 0.56 and 0.44, respectively, and I and D allele frequencies for the t-PA I/D polymorphism were 0.58 and 0.42, respectively. Allele and genotype frequencies differed somewhat among ethnic groups. However, in the ethnic groups with the largest sample sizes (Caucasians, African Americans), allele and genotype frequencies did not differ substantially from previous values in larger populations. The genotype distributions for both polymorphisms were in Hardy-Weinberg equilibrium. The distribution of men and women, and women who were on and not on HRT, did not differ among the three genotype groups at each of the two gene loci.

Baseline characteristics and PAI-1 4 G/5 G genotype (Table 2)

At baseline, PAI-1 genotype groups did not differ in terms of body weight, or $\dot{V}O_{2max}$, although 4 G and 5 G homozygous individuals had significantly higher BMI than heterozygotes. Baseline PAI-1 activity, t-PA activity, and t-PA antigen levels also were not significantly different among PAI-1 genotype groups either with or without covarying for BMI and $\dot{V}O_{2max}$.

Baseline characteristics and t-PA I/D genotype (Table 3)

At baseline, there were no differences in body weight, BMI, or $\dot{V}O_{2max}$ among t-PA genotype groups. Baseline t-PA activity and antigen levels also did not differ significantly among the t-PA genotype groups, again either with or without covarying for baseline PAI-1 activity, BMI, and $\dot{V}O_{2max}$.

Overall exercise training effects

In the total group, exercise training resulted in significant increases in $\dot{V}O_{2max}$ (3.8 ± 0.5 mL/kg/min, 0.26 ± 0.04 L/min; $p < 0.0001$) and decreases in body weight (−1.6 ± 0.4 kg, $p < 0.001$) and BMI (−0.55 ± 0.12 kg/m², $p < 0.001$). Exercise training resulted in no change in PAI-1 activity (−0.43 ± 0.81 IU/mL), increased t-PA activity (0.37 ± 0.16 IU/mL, $p = 0.02$), and decreased t-PA antigen levels (−0.88 ± 0.20 ng/mL, $p < 0.001$). In the total group, PAI-1 activity changes with training were positively correlated with training-induced changes in t-PA antigen ($r = 0.73$, $p < 0.001$). No significant correlations were found between training-induced changes in fibrinolytic variables and changes in body composition. Changes in $\dot{V}O_{2max}$ with training were negatively correlated with training-induced changes in PAI-1 activity ($r = -0.30$, $p = 0.043$) and t-PA antigen ($r = -0.31$, $p = 0.042$).

Table 1 PAI-1 and t-PA gene allele frequencies for the total study population and the Caucasian and African American ethnic groups

	PAI-1 Alleles		*t-PA Alleles*	
	4 G	*5 G*	*I*	*D*
Total study population	0.56	0.44	0.58	0.42
Caucasians	0.62	0.38	0.64	0.36
African Americans	0.30	0.70	0.35	0.65

Table 2 Baseline and final physical characteristics and fibrinolysis values for PAI-1 genotype groups

	PAI-1 Genotype Groups		
	4 G/4 G (n = 15)	*4 G/5 G (n = 20)*	*5 G/5 G (n = 10)*
Age, yr	58.3 ± 1.6	58.1 ± 1.4	57.7 ± 1.9
Body weight, kg			
– *baseline*	87.3 ± 3.9	77.2 ± 2.6	84.5 ± 4.0
– *final*	85.7 ± 3.7	75.7 ± 2.6	82.6 ± 3.8
– *change*	−1.6 ± 0.8	−1.4 ± 0.5^{+}	−1.9 ± 0.4^{++}
BMI, kg/m²			
– *baseline*	29.4 ± 1.0*	26.5 ± 0.8	30.3 ± 1.4*
– *final*	28.9 ± 1.0*	26.0 ± 0.7	29.7 ± 1.3*
– *change*	−0.5 ± 0.3	−0.5 ± 0.2$^{'}$	−0.7 ± 0.1^{++}
$\dot{V}O_{2max}$, ml/kg/min			
– *baseline*	24.6 ± 1.2	26.5 ± 1.2	22.8 ± 1.7
– *final*	27.9 ± 1.5	31.5 ± 1.6	25.0 ± 2.3*
– *change*	3.2 ± 0.6^{+++}	5.0 ± 0.9$^{'++}$	2.3 ± 0.7^{+}
PAI-1 activity, IU/mL			
– *baseline*	16.4 ± 1.6	13.1 ± 0.9	15.4 ± 2.0
– *final*	15.3 ± 1.5	13.3 ± 1.1	15.0 ± 2.0
– *change*	−1.1 ± 1.1	0.1 ± 1.3	−0.5 ± 2.2
t-PA activity, U/mL			
– *baseline*	0.49 ± 0.08	0.60 ± 0.08	0.54 ± 0.06
– *final*	0.87 ± 0.14	1.09 ± 0.35	0.63 ± 0.14
– *change*	0.38 ± 0.11**	0.50 ± 0.34	0.09 ± 0.15
t-PA, antigen, ng/mL			
– *baseline*	8.3 ± 1.0	7.6 ± 0.6	7.9 ± 0.9
– *final*	7.3 ± 0.9	6.7 ± 0.5	7.3 ± 0.7
– *change*	−1.0 ± 0.3^{++}	−0.9 ± 0.3^{+}	−0.6 ± 0.4

* indicates difference from 4 G/5 G genotype group significant at $p < 0.05$; $^{+}$ indicates change as a result of exercise training within that genotype group significant at $p < 0.05$, $^{'+}$ at $p < 0.01$, and $^{+++}$ at $p < 0.001$

Table 3 Baseline and final physical characteristics and fibrinolytic values for t-PA genotype groups

	t-PA Genotype Groups		
	I/I (n = 14)	I/D (n = 24)	D/D (n = 7)
Age, yr	57.6 ± 1.6	57.0 ± 1.2	62.7 ± 2.1
Body weight, kg			
– baseline	86.6 ± 3.5	81.5 ± 3.0	75.7 ± 2.8
– final	84.7 ± 3.6	80.0 ± 2.8	74.4 ± 2.9
– change	−1.9 ± 0.8*	−1.5 ± 0.4**	−1.4 ± 0.9
BMI, kg/m²			
– baseline	29.9 ± 0.7	27.6 ± 1.0	27.5 ± 1.1
– final	29.2 ± 0.8	27.1 ± 0.9	27.0 ± 1.0
– change	−0.6 ± 0.3*	−0.5 ± 0.1**	−0.5 ± 0.3
$\dot{V}O_{2max}$, ml/kg/min			
– baseline	25.1 ± 1.4	25.8 ± 1.1	22.5 ± 1.2
– final	28.5 ± 1.8	29.8 ± 1.6	26.4 ± 1.8
– change	3.4 ± 0.7***	4.0 ± 0.8***	4.0 ± 0.9**
t-PA activity, U/mL			
– baseline	0.45 ± 0.05	0.62 ± 0.08	0.50 ± 0.06
– final	0.82 ± 0.13	1.1 ± 0.30	0.45 ± 0.09
– change	0.38 ± 0.10**	0.48 ± 0.28	−0.05 ± 0.07
t-PA, antigen, ng/mL			
– baseline	8.2 ± 0.9	7.8 ± 0.6	7.3 ± 1.1
– final	7.4 ± 0.8	6.7 ± 0.5	7.5 ± 0.7
– change	−0.8 ± 0.3*	−1.2 ± 0.2***	0.2 ± 0.7

* indicates change as a result of exercise training within that genotype group significant at $p < 0.05$, ** at $p < 0.005$, and *** at $p < 0.001$

Exercise training and PAI-1 4 G/5 G genotype (Table 2)

There were no significant differences in training-induced changes in $\dot{V}O_{2max}$, body weight, or BMI among the three PAI-1 genotype groups. Exercise training did not alter PAI-1 activity levels differently among the three PAI-1 genotype groups. t-PA activity and t-PA antigen changes with training were not significantly different among PAI-1 genotype groups, either with or without adjusting for gender and training-induced changes in body weight, BMI, and $\dot{V}O_{2max}$. However, significant t-PA antigen reductions with training were evident only in PAI-1 4 G allele carriers and significant t-PA activity increases with training were evident only in PAI-1 4 G homozygotes. These same PAI-1 genotype-dependent differences in t-PA antigen and activity training responses were still evident when analyzed only in the Caucasian subjects.

Exercise training and t-PA I/D genotype (Table 3)

There were no significant differences in the training-induced changes in body weight, BMI or $\dot{V}O_{2max}$ among the three t-PA genotype groups. The genotype-dependent training-induced t-PA antigen ($p = 0.054$), but not t-PA activity ($p = 0.51$), responses approached statistical significance. However, after covarying for baseline t-PA antigen levels, t-PA genotype significantly affected the training-induced improvement in t-PA antigen levels ($p = 0.033$). t-PA activity and t-PA antigen levels did not change significantly with training in t-PA D/D genotype individuals, whereas t-PA I/I genotype individuals increased t-PA activity ($p = 0.003$) and decreased t-PA antigen levels ($p = 0.015$) with training. In addition, a decrease in t-PA antigen levels with training was also observed in the t-PA I/D heterozygotes ($p < 0.0001$). Post hoc analyses indicated that the change in t-PA antigen levels in the D/D genotype group was significantly different from that in the I/D heterozygotes ($p = 0.011$). The effect of t-PA genotype on changes in t-PA antigen levels approached significance after covarying for training-induced changes in PAI-1 activity levels ($p = 0.052$). Changes in t-PA activity with training were not different among t-PA genotypes after controlling for changes in PAI-1 activity. Again, the same general trends for t-PA genotype-dependent training-induced t-PA antigen and activity changes were evident when the analyses were run only on the Caucasian subjects.

Discussion

The novel finding of the present study is that in older healthy sedentary men and women at risk for CV disease, the exercise training-induced change in t-PA antigen levels is associated with the I/D gene variant in intron 8 of the t-PA gene. The t-PA I/D heterozygotes demonstrated a larger reduction in t-PA antigen levels with exercise training than D allele homozygotes. D/D homozygotes also did not elicit significant changes in either t-PA activity or t-PA antigen with training. In addition, there was some evidence that PAI-1 genotype might affect t-PA antigen levels with exercise training.

Prospective studies [22,23] have found an increased risk for both MI and stroke in those with elevated t-PA levels. Common genetic variants associated with t-PA levels have recently been widely studied. In agreement with previous reports [16,23,28], we found baseline t-PA activity and antigen levels were not related to the I/D polymorphism in intron 8 of the t-PA gene. This polymorphism does not appear to influence basal t-PA production by endothelial cells [27]. However, it has recently been reported that this polymorphism is associated with t-PA vascular release rate in vivo [17]. To our knowledge, the present study is the first to show that exercise training-induced changes in t-PA antigen were significantly associated with this t-PA I/D polymorphism, with the greatest reduction in t-PA antigen levels evident in I/D heterozygotes, while no significant change was evident in D homozygotes. Thus, the present findings provide support for the existence of significant gene-environment (exercise) interactions that modify systemic fibrinolysis. However, the t-PA I/D polymorphism is intronic and, hence, can not be functional. Thus, our finding, that this polymorphism affected training-induced t-PA antigen changes, may be the result of this locus actually being in linkage disequilibrium with an as yet unknown functional variant within this gene.

The PAI-1 gene has been studied extensively and substantial evidence indicates that a functional molecular mechanism is responsible for the genotype-dependent differential PAI-1 production. The 4 G/5 G polymorphism is located in the promoter region of the gene, and both the 4 G and 5 G alleles contain binding sites for a transcription activator [5,10]. However, the 5 G allele also provides a binding site for a transcription repressor. Importantly,

the site for transcription repressor binding partially overlaps the site for transcription activator binding. Thus, the two transcription factors compete with each other for binding. This has been proposed as the mechanism for the 4 G allele being associated with higher PAI-1 production [5].

Despite some studies reporting an association between the PAI-1 promoter polymorphism and circulating PAI-1 levels [9,30], in agreement with others [7,13], our subject's baseline PAI-1 activity levels were not associated with the 4 G/5 G PAI-1 promoter polymorphism. This lack of an association may be due to the fact that plasma PAI-1 activity is dynamic and involves not only its basal production, but also binding to the plasminogen activators and clearance from the systemic circulation, in addition to a conversion to its latent conformation. A recent study reported an association between t-PA levels and PAI-1 genotypes [14]. In the present study, neither baseline t-PA antigen levels nor t-PA activity was associated with PAI-1 4 G/5 G genotype, a finding that might be attributable to the relatively small sample size we had to detect such a relationship. A previous investigation reported that regular exercise may be more beneficial to the 4 G homozygotes as those individuals showed a significant reduction in PAI-1 activity with training [26]. These previous results are similar to ours as we demonstrated a possible favorable effect of exercise training by reducing t-PA antigen up to 12% in the 4 G/4 G and 4 G/5 G groups and by increasing t-PA activity by 78% in the 4 G/4 G and 83% (though not significant) in the 4 G/5 G, despite a non-significant change in PAI-1 activity. In contrast, individuals in the 5 G homozygous group did not show significant changes in t-PA antigen nor t-PA activity. This suggests a potential role for the PAI-1 4 G/5 G polymorphism in determining exercise training-induced changes of endogenous fibrinolysis. On the other hand, despite some reports that the PAI-1 4 G/5 G polymorphism may be a candidate locus for obesity, although BMI at baseline was related to PAI-1 genotype in our study, the heterozygotes at this locus had the lowest BMI compared to both homozygote groups and it is difficult to ascribe physiological significance to such a relationship.

There is evidence, although not completely consistent, that t-PA antigen is a better marker of fibrinolysis [23]. The half-life of active t-PA and PAI-1 is rather short (5 – 7 minutes). In addition, t-PA/PAI-1 complex clearance is much slower than free t-PA, and hence, the t-PA/PAI-1 complex has a longer half-life. Therefore, when the PAI-1 level is high, t-PA antigen could still be accumulating in the circulation, making it a more stable marker of impaired fibrinolytic potential. Since the majority of t-PA measured by the antigenic assay is in the form of t-PA/PAI-1 complex, the t-PA antigen levels, as determined in the present study, would primarily reflect the levels of PAI-1. In addition, it has been shown that although circadian variations in t-PA antigen exist, the changes are much smaller than those of PAI-1 and t-PA activities. Moreover, t-PA antigen levels show smaller intra-individual variation compared to PAI-1 and t-PA activity measures. Thus, the finding that a decrease in t-PA antigen levels with exercise training occurs in the subjects carrying the 4 G alleles may be of particular importance in terms of CV disease and stroke risk reduction with exercise training in those with the 4 G/4 G and 4 G/5 G genotype.

Sample size may be a limitation when interpreting our results. However, a number of study design features enhanced our ability to reduce inter-individual variance in baseline fibrinolytic measures and their responses to exercise training, including the control of diet, which can have it's own independent effects on fibrinolytic measures, the screening of participants to exclude those with any evidence of CV disease or recent inflammation or infection, the recruitment of sedentary individuals to eliminate any potential effect of varying physical activity levels on fibrinolysis, the application of a highly standardized and supervised prolonged endurance exercise training intervention, and the assessment of three, rather than a single, fibrinolytic indices. These design features undoubtedly enhanced our ability to detect genotype-dependent differences by accounting for other variables known to contribute to the inter-individual variability in these fibrinolytic indices.

In summary, we found that t-PA antigen, a CV disease risk factor, may be differentially modified by exercise training in older healthy sedentary men and women depending on their t-PA I/D genotype. It appears that t-PA I allele carriers improved t-PA activity and t-PA antigen levels with exercise training, while t-PA D allele homozygotes generally did not elicit improvements with exercise training. If this is substantiated in a larger prospective trial, since there is no specific medication to improve fibrinolysis, t-PA I allele carriers would appear to especially benefit from exercise training in terms of improving their fibrinolytic capacity. Our data also suggest a potential role for the PAI-1 4 G/5 G polymorphism in determining exercise training-induced changes of endogenous fibrinolysis.

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